REMARKS

This response is submitted with a Request for Continued Examination ("RCE"), and assumes entry of the January 18 Amendment and consideration of the remarks set forth therein. Claims 1, 5, 6, 10 and 14-65 are pending in the application. The Applicants note with appreciation the Examiner's detailed analysis set forth in the Advisory Action regarding the pending claims. This Supplemental Response addresses the issues raised therein.

The Applicants acknowledge the comments in the Advisory Action indicating that the amendments to claims 16, 19, 28 and 38-40, and new claims 58-65, require a new search and further consideration. The concurrently filed RCE provides the Examiner with the opportunity to perform such further search and consideration.

Issues under 35 U.S.C. § 112, First Paragraph

The Advisory Action indicates that the amendments to claims 16, 19, 28 and 38-40 raise new issues under 35 U.S.C. § 112, ¶ 1 in that the claims allegedly fail to meet the written description requirement. Specifically, the Advisory Action alleges that the amended claim elements relating to (1) a fragment that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50 and (2) a fragment that will hybridize under low or high stringency conditions to nucleotides 56-117 of SEQ ID NO:55, encompass genera that are beyond the scope of the disclosure.

The Examiner's suggestion to incorporate the SEQ ID NOs. of exemplary sequences into the claims was adopted in the January 18 Amendment. As discussed in that Amendment, the Applicants respectfully submit that the specification includes a full written description for the entire scope of the various claim elements.

For a claim drawn to a genus, the written description requirement is satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, or by functional characteristics coupled with a known or disclosed correlation between function and structure. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement, 66 (4) Fed. Reg. 1099, 1106, January 5, 2001 (hereinafter "the Guidelines").

The January 18 Amendment changed the recitation of the claim element relating to a first nucleic acid fragment that enhances translation of a first cold shock inducible gene under cold shock conditions (the upstream box) to a nucleic acid fragment comprising SEQ. ID NO:48, SEQ. ID NO:49, SEQ. ID NO:50 or a fragment that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50. The specifically defined sequences are complimentary to the region from nucleotide 1023-1035 of the *E. coli* 16S rRNA. (See, page 52, lines 9-10 of the specification.) Each of SEQ. ID NOs:48-50 may play a roll in enhancing translation by a mechanism similar to that of the downstream box (page 28, lines 5-8), *i.e.*, by annealing to the bacterial rRNA at positions 1023-1035. Thus, each of the exemplary species has a well defined structure (the 13 bp sequence of SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50) that is specifically correlated to its putative function (to enhance translation).

The defined structures of the sequences identified by SEQ. ID NOs:48-50 (or nucleic acid molecules hybridizing to the precise complement of SEQ. ID NOs:45-50) are believed to be correlated to the function of enhancing translation because of their putative ability to anneal to nucleotides 1023-1035 of the *E. coli* 16S rRNA. This mechanism may be similar to the

interaction of the downstream box to nucleotides 1469-1483 of the *E. coli* rRNA, which was discussed in the January 18 Amendment. (*See,* page 28, lines 3-7 of the specification.) The ability to hybridize with rRNA nucleotides 1023-1035 is directly and causally correlated to the fact that SEQ. ID NOs:48-50 are complementary to the rRNA sequence. Thus, the definition of the genus of nucleic acid fragments that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50 directly correlates structure with function.

It is respectfully submitted that one skilled in the art understands that the genus of nucleic acid fragments that will hybridize with a reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50 under the specified conditions is a finite and well defined group of fragments that are fully supported by the written description. Claims are not interpreted in a vacuum, but are part of and are read in light of the specification. *Slimfold Manufacturing Co., Inc. v. Kinkead Industries, Inc.* 1 USPQ 2d 1563, 1566 (Fed. Cir. 1987). Given a fair reading of the specification, including the clear guidance regarding hybridization conditions provided on pages 16 and 17, the skilled artisan would understand that only fragments which are structurally similar to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50 would hybridize to the reference nucleic acid molecule that is precisely complimentary to one of the enumerated SEQ. ID NOs. In specific response to the allegation set forth in the Advisory Action that a nucleic acid molecule sharing only one common nucleotide with the reference molecule would hybridize, one skilled in the art would understand that this is not so. Instead, given the specification's guidance on what constitutes low and high stringency conditions, the skilled artisan would recognize that significant structural similarity must be present for hybridization to occur.

The Examples provided in the *Revised Interim Written Description Guidelines Training Materials*, which is available on the Patent and Trademark Office Internet website at http://www.uspto.gov/web/offices/pac/writtendesc.pdf (hereinafter, "Written Description Examples") are instructive with respect to the issue. Example No. 9 relates to a claim directed to "[a]n isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity."

The claim of Example 9 in the Written Description Examples is similar to a recitation in present claim 16 that is exemplary of the element at issue, which reads in relevant part, "a first nucleic acid fragment comprising SEQ. ID NO:48, SEQ. ID NO:49, SEQ. ID NO:50 or a fragment that will hybridize under low or high stringency conditions to a reference nucleic acid molecule that is precisely complementary to SEQ. ID NO:48, SEQ. ID NO:49 or SEQ. ID NO:50, ... wherein said first nucleic acid fragment enhances translation of [a] first cold shock inducible gene transcript under conditions that elicit the cold shock response in bacterium".

Both Example 9 and present claim 16 define a nucleic acid in terms of its ability to hybridize with the compliment of a specifically defined sequence. Also, both Example 9 and claim 16 couple this characteristic with a known function: coding of a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity (Example 9), or enhancing translation of the first cold shock inducible gene transcript under conditions that elicit the cold shock response (present claim 16). Therefore, the reasoning set forth in the Example 9 analysis is applicable to present claims 16, 19, 28 and 38-40 as well. According to Example 9, the specification discloses a single cDNA (SEQ ID NO:1) which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. Recognizing that hybridization

techniques using a known DNA as a probe under highly stringent conditions are conventional in the art, the analysis and conclusion set forth in Example 9 reads, in relevant part, as follows:

> The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity.
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> ***
>
> There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.
>
> There is actual reduction to practice of the disclosed species.
>
> Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.
>
> **Conclusion**: The claimed invention is adequately described.

Applying the teachings of Example 9 to the element of present claim 16, this application discloses three specific species in the form of SEQ. ID NO:48, SEQ. ID NO:49 and SEQ. ID NO:50. Analogous to Example 9, the claim is directed to a nucleic acid vector having a genus of nucleic acids, all of which must hybridize with at least one of the recited sequences and must perform the specific function of translational enhancement. Also like Example 9, there is an actual reduction to practice of the disclosed species. (*See, e.g.*, page 52, line 12 – page 53, line 7

of the specification.) As such, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claim because the hybridization conditions set forth in the claim, which are described in the specification at pages 16-17 and which are specifically recited in dependent claim 58, would yield structurally similar DNAs. Thus, like in Example 9, a representative number of species is disclosed, since the claimed hybridization conditions in combination with the recited translational enhancing function and the level of skill and knowledge in the art are adequate to determine that the Applicants were in possession of the claimed invention. Thus, claim 16 (and the specific element discussed above) meets the written description requirement.

The Advisory Action also alleges that the written description does not fully encompass the scope of the genus of nucleic acids that will hybridize to nucleotides 56-117 of SEQ ID NO:55 under low or high stringency conditions. This element is presented, among other places, in claim 19. As discussed above, one skilled in the art would understand the meaning and scope associated with low and high stringency hybridization conditions, and would also understand the function of nucleotides 56-117 based on a fair reading of the specification. Specifically, a review of pages 26, lines 1-18, Example 8 on pages 47-49, and page 54, lines 10-17 would convey to the skilled artisan that nucleotides 56-117 serve to repress expression of a cold shock gene at 37°C. Example 8 of the specification also describes plasmids pMM022, pMM023 and pMM026, all of which include nucleotides 56-117 of the 5' UTR of CspA.

The element of claim 19 defined as the genus of nucleic acid fragments that will hybridize to a reference nucleic acid molecule that is precisely complementary to nucleotides 56-117 under low or high stringency conditions can also be compared favorably to Example 9 of the Written Description Examples. The claimed genus of fragments performs the specific function

of repressing expression of a gene in which it is present, which function is described in detail in the specification. Analogous to Example 9 of the Written Description Examples, plasmids pMM022, pMM023 and pMM026 were made that include a species of the genus at issue (fragments that will hybridize to nucleotides 56-117 of SEQ ID NO:55 under low or high stringency conditions). A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claimed genus because the hybridization conditions set forth in the claim (which, as noted above, are defined in the specification at pages 16-17 and are specifically recited in dependent claim 59) would yield structurally similar nucleic acids. Thus, like in Example 9, a representative number of species is disclosed, since the claimed hybridization conditions in combination with the recited gene expression repressing function and the level of skill and knowledge in the art are adequate to determine that the Applicants were in possession of the claimed invention. Therefore, the full scope of the genus of nucleic acid fragments that will hybridize to a reference nucleic acid molecule that is precisely complementary to nucleotides 56-117 of SEQ ID NO:55 under low or high stringency conditions is also supported by the written description.

For the same reasoning as set forth above, the remaining elements that are defined throughout the various claims in terms of the ability to hybridize to complements of specific sequences share the benefit of a complete written description throughout the specification. For the reasons set forth herein and in the January 18 Amendment, it is requested that the rejections based on U.S.C. 112 ¶ 1 be reconsidered and withdrawn.

Issues under 35 U.S.C. § 102

As a matter of undisputed law, the transition phrase "consisting essentially of" is partially open, meaning that a claim introduced by this phrase includes only unlisted elements that do not

materially affect the basic and novel properties of the invention. *PPG Industries Inc. v. Guardian Industries Corp.*, 48 USPQ2d 1351 (Fed Cir 1998). Any element that does materially affect the nature of the claimed subject matter is excluded. *Id.*

Claim 1 is directed to an isolated nucleic acid molecule consisting essentially of nucleotides 1-11 of SEQ. ID NO:55, nucleotides 56-117 of SEQ. ID NO:55, nucleotides 123-135 of SEQ. ID NO:55, SEQ. ID NO:49 or SEQ. ID NO:50. By operation of law, the claim covers an isolated nucleic acid molecule that includes one of the listed sequences and other components that do not affect the basic nature of the listed sequences, but no other elements that would change their basic nature.

For example, claim 1 covers a nucleic acid molecule having the sequence GCCGAAAGGCACA (nucleotides 123-135 of SEQ ID NO:55) and additional nucleotides if and only if the additional nucleotides do not change the basic nature of the sequence GCCGAAAGGCACA. The basic nature of nucleotides 123-135 of SEQ ID NO:55 is as follows: (1) it is an isolated string of nucleotides that is not incorporated into a gene and is not otherwise capable of transcribing a protein; which, (2) if and when incorporated into a gene and transcribed, will function to enhance translation of the transcript by a certain amount, but will serve no other regulatory or coding function. Any additional sequence added to the molecule having the sequence GCCGAAAGGCACA will remove the construct from the scope of the claim if the additional sequence changes this basic nature.

For example, the claim covers a nucleic acid molecule having the sequence GCCGAAAGGCACACUUAAUUAUU (nucleotides 123-145 of SEQ ID NO:55) because, as far as the Applicants are aware, the additional sequence CUUAAUUAUU does not perform any substantial regulatory or coding function. In other words, if one were to incorporate a nucleic

acid molecule having only the sequence GCCGAAAGGCACA into a gene in accordance with the teaching of the specification, one would hope to establish a gene having a certain level of enhanced translation, but otherwise no further functional modifications. If one instead incorporated GCCGAAAGGCACACUUAAUUAUU into the gene, one would hope to establish exactly the same result. Thus, the additional sequence CUUAAUUAUU does not affect the basic nature of the molecule.

On the other hand, the claim would not cover a nucleic acid molecule having the sequence GCCGAAAGGCACACUUAAUUAUUAAAGGUAAUA (nucleotides 123-155 of SEQ ID NO:55) because that sequence is believed to include the Shine-Dalgarno sequence. Because the Shine-Dalgarno sequence could potentially enhance translation above and beyond the level of nucleotides 123-135 alone, the Shine-Dalgarno sequence affects the basic nature of the molecule. Thus, the addition of the sequence AAAGGUAAUA removes the molecule from the scope of the claim. Similarly, a molecule having nucleotides 50-135 of SEQ ID NO:55 would be excluded from the claim because such molecule would include a region that represses gene expression at 37°C (nucleotides 56-117) and represents an additional regulatory region. Thus, the addition of this region also affect the basic nature of the molecule. Therefore, if one were to incorporate these molecules into a gene, one would expect the gene to have different functional characteristics than if GCCGAAAGGCACA were incorporated alone.

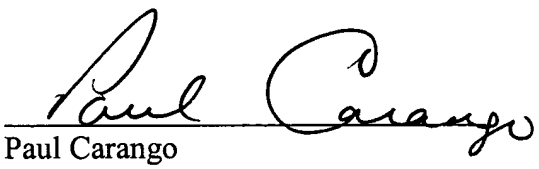
As set forth in detail in the January 18 Amendment, each of Goldstein, Oppenheim '039 and Oppenheim '169 include elements, such as a promoter, a protein coding region or other functional nucleotide sequences, that would affect the basic nature of a nucleic acid molecule having only nucleotides 123-135 of SEQ ID NO:55 (or the other sequences recited in claim 1). Therefore, the cited references do not anticipate claim 1. Moreover, because the references

include no suggestion to isolate the molecules recited in claim 1, the references also do not render the claim obvious. Thus, it is requested that the rejection of claim 1 and its dependent claims 5, 6, 10, 14 and 15 be reconsidered and withdrawn.

Conclusion

For the foregoing reasons, it is respectfully requested that all of the rejections and objections set forth in the Office Action and Advisory Action be reconsidered and withdrawn. It is believed that the application is now in condition for allowance, which action is solicited. If the Examiner believes that minor amendments or other action will advance the case, the Examiner is invited to telephone the Applicants' undersigned attorney.

Respectfully submitted,



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